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A Randomized Clinical Trial of a Decision Aid and Values Clarification Method for Parents of a Fetus or Neonate Diagnosed with a Life-Threatening Congenital Heart Defect

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Abstract

Introduction: Parents who receive the diagnosis of a life-threatening, complex heart defect in their fetus or neonate face a difficult choice between pursuing termination (for fetal diagnoses), palliative care, or complex surgical interventions. Shared decision making (SDM) is recommended in clinical contexts where there is clinical equipoise. SDM can be facilitated by decision aids. The International Patient Decision Aids Standards collaboration recommends the inclusion of values clarification methods (VCMs), yet little evidence exists concerning the incremental impact of VCMs on patient or surrogate decision making. This protocol describes a randomized clinical trial to evaluate the effect of a decision aid (with and without a VCM) on parental mental health and decision making within a clinical encounter.

Methods and Analysis: Parents who have a fetus or neonate diagnosed with one of six complex congenital heart defects diagnosed at a single tertiary center will be recruited. Data collection for the prospective observational control group was conducted September 2018 to December 2020 (N=35) and data collection for two intervention groups is ongoing (began October 2020). At least 100 participants will be randomized 1:1 to two intervention groups (decision aid only vs. decision aid with VCM). For the intervention groups, data will be collected at four time points: 1) at diagnosis, 2) post-receipt of decision aid, 3) post-decision, and 4) 3-months post-decision. Data collection for the control group was the same, except they did not receive a survey at Time 2. Linear mixed effects models will assess differences between study arms in distress (primary outcome), grief, and decision quality (secondary outcomes) at 3-months post-treatment decision.

Ethics and Dissemination: This study was approved by the University of Utah Institutional Review Board and the protocol is published on ClinicalTrials.gov (NCT04437069). Study findings will be presented at national conferences and with scientific research journals.

Article Summary

Strengths and limitations of this study:

- One study strength is that this is a randomized clinical trial design with clinically relevant, validated outcome measures.
- A second strength is that this study will add to the limited literature on the effectiveness of value clarification methods in real-word clinical contexts.
- Given that the study takes place at one tertiary center, there is potential limitation of a small sample size and reduced power for analyses.

Introduction

Background and rationale

Congenital heart disease occurs for about 40,000 live births per year; of these, about 2-3% are life-threatening congenital heart defects (CHDs).[1-3] Even with early intervention those diagnosed with life-threatening CHDs have frequent readmissions, require additional interventions and typically face a shortened life span.[4] A diagnosis of a severe, life-threatening CHD in a fetus or neonate is an unexpected and emotionally distressful event for parents who must then decide between termination (when diagnosed prenatally), palliative care, or surgery.[5-8] Parents experience significant grief,[9, 10] distress, depression, and anxiety[11-13] surrounding this difficult decision, which can compromise their mental health.[14-16] Providers, ethicists, and parents may perceive clinical equipoise on which treatment option (i.e., termination, palliative care, or surgery) is best for the family.[17-19]

Shared decision making (SDM) is an approach for supporting patient engagement with clinicians that is particularly useful for contexts, such as life-threatening CHD, which involve clinical equipoise and value-laden, complex decisions.[20, 21] Decision aids are tools that improve the SDM process and include information on treatment options that are evidence based, balanced and help people clarify their values.[4, 22] Decision aids increase patients' knowledge, and engagement related to the diagnosis and treatment decision making. In addition, studies have found greater concordance between patients' preferences and treatment received, improved patient-provider communication, and reduced uncertainty and decisional conflict in those receiving decision aids.[23]

The International Patient Decision Aids Standards (IPDAS) Collaboration developed criteria for a well-designed decision aid.[24] Values clarification methods (i.e., processes that aid patients in clarifying their values and goals in order to improve alignment between their preferences and their treatments) were included as a critical component. Although some studies have found positive effects of value clarification methods on decision outcomes, there are few rigorous studies in real-world clinical contexts that evaluate whether value clarification methods improve key outcomes, prompting calls for additional research.[24-26]

Objectives & Hypothesis

The main objective of the study is to evaluate the effect of a decision aid with and without a values clarification method on longitudinal parent mental and physical health, decision-making, and clinical encounter outcomes (e.g., quality of clinician consultation and risk communication). Since no prior data on decision aid use in CHD exist, we will also compare parents who receive the decision aid to parents who do not (prospective observational control group enrolled during decision aid development) on the aforementioned outcomes.

We hypothesize that parents who receive the decision aid with the values clarification method will report less distress (primary outcome), reduced grief, and better decision quality (secondary outcomes) relative to participants who receive the decision aid only across 3-months post treatment decision. We also hypothesize that participants who receive the decision aid with or without the values clarification method will report reduced distress, grief, and better decision quality relative to participants who are in the prospective observational control group.

We will also test the impact of the decision aid with a values clarification method on several exploratory measures (e.g. self-efficacy, satisfaction, and decision regret).

Methods

Study Design

This is a randomized clinical trial examining the effectiveness of a decision aid and values clarification method. There are two intervention groups and one prospective observational control group. Data collection for the prospective observational control group was conducted September 2018 – December 2020 (N= 35) and data collection for the intervention groups (the primary analytic sample) began October 2020 and is ongoing. The flow of the study is outlined in Figure 1.

Study Setting

This is a single site study at a children's hospital in the Intermountain West. Physicians at this hospital perform >650 fetal echocardiograms with about 125 new complex CHD diagnoses annually.

Participants and Eligibility Criteria

To be eligible for the study, parents must be 18+ who have a fetus or neonate diagnosed with a complex, life-threatening CHD (whether prenatally or postnatally). While the decision aid was being developed, the control group was recruited with these guidelines. The decision aid was developed to provide information on the following six CHD diagnoses: truncus arteriosus with greater than moderate truncal valve regurgitation, pulmonary atresia with intact ventricular septum with a severely hypoplastic right ventricle that will require single ventricle palliation, complex single ventricle, complex single ventricle with heterotaxy, hypoplastic left heart

syndrome (HLHS), and Ebstein anomaly of the tricuspid valve with greater than moderate regurgitation. These diagnoses were chosen as they were deemed preference sensitive in that surgical intervention, palliative care, and termination were all medically reasonable treatment options by expert consensus. Thus, in order to be eligible for one of the two intervention groups, the fetus/neonate must be diagnosed with one of the six aforementioned diagnoses.

Recruitment and Consent

When a fetus/neonate is diagnosed with a qualifying CHD, a pediatric cardiologist will evaluate the diagnosis to confirm eligibility for the study. When an eligible fetus/neonate is identified, the parent(s) will be approached by the study team and invited to participate in the study. One or both parents may participate. Those interested will receive a link to complete the informed consent through an electronic data capture (REDCap). If both parents consent to participation, they will receive separate links to complete their own informed consent and surveys.

Randomization

Participants will be randomized using REDCap (HIPAA-compliant remote data capture system) into one of two intervention groups, described below, after completing the baseline survey. Participants will not be explicitly told which group they were randomized to. Both intervention groups will receive the same decision aid, but one arm will receive a values clarification method integrated within the decision aid, while the other group will get the decision aid without the values clarification method. The decision aid is an app on an Amazon Fire tablet, which is either given to the parent(s) in clinic if they complete the baseline survey and consent in person, or is mailed to their home if they complete the consent outside of clinic. The tablet remains in their possession for the duration of the study so that they can consult the decision aid as often as they would like.

Development of Decision Aid and Values Clarification Method

We used data from focus groups of parents who had a fetus or neonate diagnosed with a complex CHD, as well as semi-structured interviews with family and provider stakeholders to identify important content to include in the digital decision aid.[27, 28] The tool was developed through an iterative process of content drafting by the development team followed by multiple rounds of content review and revision with the research team, parent partners, and healthcare providers in relevant fields (e.g., pediatric cardiologists, surgeons, social workers, palliative care experts). The team gathered stories about parents' experiences during several individual and group interviews.

The research team also developed a values clarification method. We began by examining qualitative data from the focus group and interviews related to factors influencing parents' choices and identifying key elements that had influenced parents' decision. The team then engaged in multiple workshop sessions, discussing how best to describe components of each value, with parent partners providing input on draft versions of these descriptions. The values clarification method interface was developed through an iterative process of creating alpha versions, testing, and revision.

Patient involvement

Three parents (two females and one male) whose children were diagnosed with complex CHD were invited to serve as parent collaborators. Discussions with these parents informed the design and development of the decision aid, outcome measures that were chosen, and methods of recruitment for the study.

Interventions and Comparators

Prospective Observational Control Group

Participants in the prospective observational control group did not receive the decision aid or values clarification method. Participants were enrolled during the development of the decision aid to prevent contamination by providers or other families exposed to the decision aid. Participants received standard clinical care.

Decision Aid

The intervention group participants receive a decision aid after diagnosis, and then continue with the standard care. The decision aid includes eight sections, which are broadly described in Table 1. Section 5 is individualized to each participant to show information specific to their fetus/neonate's diagnosis. The decision aid is an app that is loaded onto an Amazon Fire tablet, which is given to participants.

Values Clarification Method

The Values Clarification Method is designed to help participants clarify the choice that feels better for them and their family. For those randomized to receive the values clarification method, the decision aid includes an extra module with the following content:

What Matters Most to You. The goal of this exercise is to help participants think through some long term and short term consequences of their decision. When faced with a life-threatening diagnosis, there are many consequences to consider, and participants may not know how they feel about each of them or how to weigh them by importance or value. To begin, participants choose two of the possible treatment decision options (surgery, comfort care, and ending the pregnancy) and compare them in 10 different topic areas. Some examples of the topics are: time in the hospital, the risk that the child will have impairments, financial issues, and life in adulthood. The purpose of choosing two potential decisions at a time is to put them on a clear spectrum in a preference scale, as weighting all three at once would be too complicated in terms

of determining weights. For each topic, there is a sliding scale between the two choices where they drag the slider to show how much they prefer one choice over another. At the end, they are shown a summary of which choice they preferred for each category. They are not issued a definitive result; the values clarification method allows them to look at a summary of their choices and draw their own conclusion about what they chose. Participants may repeat the exercise, selecting other options to compare.

After the interventions were developed in English, the decision aid and values clarification method were translated into Spanish by certified translators in the University of Utah's Office of Research Participant Advocacy (as were consent documents and survey measures).

Outcomes

All study measures were categorized into three conceptual domains: parental mental and physical health, decision-making quality, and clinical encounter (e.g., consultation quality) in Table 2. The primary outcome is distress, measured by the Brief Symptom Inventory Global Severity Index.[29] The co-secondary outcomes are perinatal grief and decision quality (i.e., adequate knowledge and concordance between participants' preferences and treatment decision).[30, 31] Additional exploratory outcomes will also be measured. Descriptions of all study measures and time points for survey data collection are included in Table 2. Parent characteristics will be examined as potential covariates.

Sample Size and Power Calculation

At least 100 families will be randomized 1:1 to the two intervention groups, allowing up to two parents to participate per fetus/neonate. Our sample size calculations were based on the primary comparison between DA with and without the VCE. Based on our previous work,[32] we assume ≥ 80% retention, a 3-month pre-post R ≥ 0.5, an average of ≥ 1.75 participating parents per

participating family, an intra-class correlation (ICC) between parents in the same family ≤ 0.50, and ≥ 50 families randomized to each of the intervention groups (decision aid only and decision aid with values clarification method). Using these assumptions, the mixed effects model will provide 80% power with 2-sided α=0.05 to detect a mean difference in the primary outcome, distress, equal to 0.50 of 1 standard deviation. This represents a moderate effect size in Cohen's terminology.[33] Assuming a pooled SD in the global distress of 0.56 units,[32] the 0.50 SDs represents a minimum detectable effect of 0.28 units.

Data Collection

Potentially eligible parents are identified and approached by a study team member who is trained in interacting with people who are going through highly emotional medical events. If the parents are deemed to be under too much distress, they are not approached. If the parents are deemed approachable by the trained staff, the study is presented using an informational pamphlet, and the potential participant(s) are encouraged to follow the link or QR code on the pamphlet if they would like to participate in the study. The parents who were given the link are recorded in a recruitment tracker. All parents who follow the link on their own are consented to participate in the study and recorded in REDCap. This usually happens with parents whose fetuses are prenatally-diagnosed, and they follow the link from their home electronic devices. If the neonate was postnatally-diagnosed, the parents are approached in the same manner in the hospital and are given the opportunity to consent and participate in the study using a tablet in person. Parents who are found to be ineligible or who decline participation will be recorded along with the reason.

Data Abstraction

When screening for eligibility, the fetus/neonate diagnosis (verified by a pediatric cardiologist) and date of diagnosis will be abstracted. Once enrolled in the study, gestational age at birth, the

presence of other syndromes/birth defects, and the dates of surgery (if applicable) will be abstracted from the medical record and documented. Further surgery dates will be recorded by the research coordinator.

Surveys

Participants in the prospective observational control group filled out surveys at three time points: 1) Baseline, 2) Post-Decision, and 3) Three Months Post-Decision (see Table 1 for an overview of measurements). There are four survey time points for the intervention groups: 1) Baseline, 2) Post-Viewing of the Decision Aid (or Decision Aid and Values Clarification Method) but prior to making the decision, 3) Post-Decision, and 4) Three Months Post-Decision. Surveys are administered via REDCap by sending an email to the participant with a survey link. Participants may request paper surveys to be mailed to them. If the participant does not access the survey link, they will be contacted by phone or in person during a routine clinic visit to ask them to fill out the survey or will be mailed a paper survey.

Data Management and Monitoring

Adverse events that occur during data collection will be recorded by the study coordinator, along with any circumstances that make particular participants unique. In this way, unanticipated data points during analysis may be explained and accounted for. Additionally, information about mental health resources are given to participants at the end of each survey, including a 24 hour, 7 days-a-week phone crisis service that is staffed by mental health professionals providing emotional support, assistance, crisis interventions, and suicide preventions to individuals experiencing emotional distress or psychiatric crisis. The social worker at the children's hospital also has their contact information listed for participants to be able to reach out.

Frequent reports will be run to detect data errors or missing data. Any issues will be addressed during a weekly meeting between the study coordinator, post-doctoral fellow(s), and the principal investigator.

Data Analysis Plan

After data collection, we will use standardized mean differences to assess balance between intervention groups in baseline levels of study endpoints and other potential prognostic baseline indicators, including participants' age, race, and comorbidities. Outcome variables exhibiting substantial skewness may be transformed to better approximate normality. All participants will be analyzed in their assigned intervention group according to intention-to-treat, irrespective of adherence to viewing the decision aid or completing the values clarification method. Although multiple outcomes will be considered, we have designated a single primary outcome (the BSI Global Severity Index of global distress, described above) and a single primary comparison time for this outcome at 3 months.[34] We do not plan formal multiple comparison adjustments for secondary and exploratory outcomes. Results for secondary and exploratory outcomes will support or qualify the analyses of the primary outcome, and will be interpreted based on the overall pattern of results with awareness that some nominally significant relationships may be false positive findings in the context of multiple analyses. If there is sufficient power to detect differences, exploratory sub-group analyses may be conducted to detect differences by factors such as pre versus post-natal diagnoses, CHD diagnosis, and provider specialty. We also do not plan formal multiple comparison adjustment for the randomized comparison between intervention groups (Decision Aid Only v. Decision Aid with Values Clarification Method) and the non-randomized comparison (Decision Aid v. Control), as these comparisons address distinct hypotheses and are thus appropriate for evaluation on a comparison wise basis.[35]

Determining Intervention Effects on Study Endpoints

Randomized Comparisons Between Intervention Groups (Decision Aid Only V. Decision Aid with Values Clarification Method). The primary outcome, distress, measured at post decision aid, post decision, and 3-month will be compared between groups by applying restricted maximum likelihood estimation to a linear mixed effects model[36] with fixed provider effects and random family effects to account for clustering of outcomes due to these factors and an unstructured residual covariance model to account for serial correlation across the three longitudinal assessments. Inclusion of fixed effects for provider is appropriate since families are randomized to the two intervention groups for each provider, and may improve statistical power by controlling for provider variation. The model will also include fixed effects for randomized assignment as well as the baseline distress.[34] Additional pre-specified covariate adjustment is not planned, as we are not aware of further baseline factors that are likely to be strongly associated with the 3-month distress once the baseline distress is accounted for.[35] However, should a prognostic baseline factor exhibit imbalance between the randomized groups, a post-hoc sensitivity analysis will be performed with covariate adjustment for that factor to assess the robustness of the results to the imbalance. The 3-month comparison will represent the primary contrast for assessing the effect of the decision support intervention. It is possible that the full mixed effects model will fail to converge due to the inclusion of separate random effects for provider and family as well as an unstructured covariate matrix for repeated assessments in the same patient. In the event the full model fails to converge, we will repeat analyses after dropping the provider random effect. If this also fails to provide convergence, the unstructured covariance model for serial correlation will be simplified.

Similar mixed effects analyses will be used for numeric secondary and exploratory outcome variables, including the perinatal grief (secondary outcome) and most of the exploratory outcomes. For binary outcomes, including the decision quality secondary outcome, we will apply generalized estimating equations (GEE) for log-binomial regression (if convergence is achieved) or modified Poisson regression[37] (if not) to compare the proportions of participants with the outcome between the intervention groups. The post-decision comparison will be the main comparison for evaluating the effects of the interventions on secondary and exploratory outcomes hypothesized to respond quickly to the decision aid (e.g. parent-provider communication, self-efficacy) while the 3-month comparison will represent the main treatment contrast for outcomes hypothesized to respond over a longer time (e.g., grief, decision regret).

Non-Randomized Comparisons of Decision Aid Only v. Control Group. The primary outcome, distress, will be compared between the groups receiving the decision aid and the control group using an extension of the linear mixed effects model described above. The model will again include fixed effects for provider and random effects for family and an unstructured covariance matrix to account serial correlation, but will be expanded to include all three treatment groups and will include not only the baseline distress measure but also timing of diagnosis, race, and literacy level as covariates to reduce bias in these non-randomized comparisons. The comparison of Decision Aid without Values Clarification Method vs. Control will represent the primary treatment comparison to evaluate the effect of the decision aid. The comparison of Decision Aid with Values Clarification Method) vs. Control will provide a secondary assessment of the combined effect of decision support and values clarification method together. Similar extensions using linear mixed models for numeric outcomes and GEE for binary or categorical outcomes

will be applied for additional non-randomized comparisons between the decision support and control groups.

*Missing Data***.** The proposed analyses of the primary and numeric secondary and exploratory outcomes apply likelihood-based inference and will thus remain approximately unbiased in the presence of missing data so long as the pattern of missingness follows a missing at random (MAR) mechanism.[38] To evaluate risk of bias from missing data patterns which depend on measured factors not included in the analytic models, participant characteristics will be compared between participants with complete data for the primary and main secondary outcomes and those participants with incomplete data. If substantial imbalances are detected, or if > 10% of participants have missing data for a primary or secondary outcome, multiple imputation will be used to impute missing outcome measurements. The multiple imputation will be performed with a Markov Chain Monte Carlo (MCMC) algorithm using an imputation model incorporating each analysis variable as well as auxiliary variables that are related to the probability of missingness.[39] Rubin's formulae will be used to account for the uncertainty introduced by the missing data. When data are missing for items within scales, we will use recommended imputation procedures rather than deleting participants listwise from the analysis.[38]

Ethics and Dissemination

This study was approved by the Institutional Review Board (IRB), and continues to be re-approved yearly according to the IRB's standards. Important modifications made to the data collection routine section of the IRB application will be reported in the findings if those changes are found to have impacted the data.

Consent to participate in the study is obtained from participants when they fill out the baseline survey. As this is a low-risk study, no signature is required. All survey data will be de-identified before sharing the results, posing no risk to participant confidentiality. Access to the data may be granted to outside parties on a case-by-case basis by the discretion of the PI. The study is registered on ClinicalTrials.gov (NCT04437069) where the public can access the full protocol. Study modifications and results will also be reported on ClinicalTrials.gov. In addition, findings will be disseminated through presentations at scientific meetings and publications in peer-reviewed journals.

Discussion

Parents of a fetus or neonate diagnosed with a life-threatening congenital heart defect are confronted with a significant and challenging decision between termination (when diagnosed prenatally), palliative care, or surgery.[5-8] This preference-sensitive decision should be supported through shared decision making whereby the family and providers can mutually engage in treatment decision making which is driven by what matters most to families and understanding of the diagnosis and treatment options.[20, 21] Decision aids are one approach to facilitate shared decision making.[40] The present study aims to evaluate the effect of a novel, family-centered decision aid on parent mental and physical health, decision-making, and clinical encounter outcomes. Few studies have examined how effective values clarification methods, which the International Patient Decision Aids Standards collaborative added as criteria for decision aids, are when combined with a decision aid in clinical contexts.[26] Therefore, this study also aims to

contribute to the literature by examining the effect of the decision aid with and without a values clarification method.

There are some potential limitations to note for this study that are common when studying pediatric conditions. There may be issues with meeting sample size requirements for sufficient statistical power. This issue could arise due to the rarity of severe CHD diagnoses and the potential for high attrition as parents are under high emotional burdens and distress surrounding the diagnosis, decision, and coping or managing the treatment they choose. Our study design attempts to proactively address these issues. For instance, we will use extensive follow-up procedures via telephone or in person to minimize attrition. If questionnaire burden results in higher than expected attrition, we will limit questions to the primary and secondary outcomes.

Our study will significantly contribute to advancing decision support and counseling for parents making life-altering decisions for their fetus or neonate with a life-threatening heart defect. This important and innovative decision aid and values clarification method will also build on the dearth of decision aids in pediatric, surrogate decision-making contexts.

Table 1. Decision Aid Content

1. *You Are Not Alone*	This introductory video (07:53 min), is intended to normalize the experience and set the stage before some of the more technical information in the tool. Key messages are: this is a difficult time for you, it's OK to cry, you didn't cause this, and you are the most qualified to make this decision. The video also describes the goals of the tool.
2. *How the Heart Works*	This section includes animations and information on the cardiovascular system, normal fetal and post-fetal heart circulation, defects that can take place during heart development that lead to abnormal heart function, and a glossary of medical terms.
3. *What is a Congenital Heart Defect?*	This section defines congenital heart defects and how they are caused and diagnosed.
4. *How We Talk About Congenital Heart Defects*	This section introduces parents to topics and terms that are often used when discussing congenital heart defects, including statistics, diagnosis variability, survival and quality of life.
5. *Learn More About Your Baby's Diagnosis*	This section shows parents individualized information specific to their fetus/baby's diagnosis. Diagnoses available in this section include Hypoplastic Left Heart Syndrome (HLHS), Complex Single Ventricle (CSV), Complex Single Ventricle with Heterotaxy (Isomerism), Pulmonary Atresia with Intact Ventricular Septum (PA/IVS), Ebstein's Anomaly of the Tricuspid Valve (With Severe Leak) and Truncus Arteriosus. Each diagnosis profile includes animated videos depicting the defect, statistics related to how common the defect is, other associated conditions, risks of having another child with the defect and expected outcomes without treatment.
6. *Learn More About Your Choices*	This is divided into three sections: Surgery, Comfort Care, and Ending the Pregnancy. Each section begins with a "What to Expect" overview and includes a description of the medical team members who may be involved, financial implications, living with this decision, and links to other websites and

	support groups. Additional information is tailored to each choice.
7. *Firsthand Experiences*	This section contains stories from parents who chose Comfort Care, Surgery or Ending the Pregnancy, in which they describe their personal experiences. Five stories are provided for each of the three choices, reflecting a variety of different outcomes. Surgery stories include examples where the child had no serious medical complications growing up, examples where the child does have complications, and examples where the child did not survive post-surgery.
8. *Questions You Can Ask Your Doctor*	This is a list of possible questions parents may wish to ask care providers. Parents can checkmark the questions they wish to take with them to their doctor, and the tool will email them just these questions. They can then either print or access their questions digitally while in their appointment.

Table 2. Study Outcomes, Descriptions, and Survey Measure Time Points

Measure	Description	Measure Timepoints			
		Time 1	Time 2	Time 3	Time 4
Primary Outcome					
Mental and Physical Health Outcomes					
Distress[29]	Basic Symptom Inventory (BSI) Global Severity Index of Global Distress: a validated scale of 53 questions that indicate the degree of stress the participant has experienced within the previous seven days. Answers range on a 5-point Likert scale from 0=not at all to 4=extremely.	X	X	X	X
Secondary Outcomes					
Decision Making Outcomes					
Perinatal Grief[30]	Twenty-seven questions measuring grief, coping, and despair following the death of a child. Rated on a 5-point Likert scale that ranges from 1=strongly disagree to 5=strongly agree.		X	X	X
Decision Quality (Values)[31]	Six questions on parent' decisional values (e.g., "How important it is to you that your child have as little pain and discomfort from treatment as possible?") rated on a 6-point Likert scale from 1=most important to 6=not as important.		X	X	X
Decision Quality (Knowledge)[31]	Twenty-six questions assessing the participants' knowledge of treatment options for CHD in two domains. The first domain regards understanding about CHD diagnosis and what the heart does, the available options, and the outcomes of comfort care. The second domain regards understanding about the outcomes of surgery/intervention and the impact of CHD on family. 21 of the questions use a dichotomous response format (either "true / false" or "yes/no"); 5 questions are multiple choice.		X	X	X

Exploratory Outcomes					
Mental and Physical Health Outcomes					
Mental and Physical Functional Health[41]	SF-12: Twelve items measuring the respondents' health across multiple dimensions. Answers rated on a 5-point Likert scale ranging from 1=excellent to 5=poor for three questions; answers are given in a dichotomous (yes/no) format for four questions; answers are given on a 6-point Likert scale ranging from 1=all of the time to 6=none of the time for three questions; answers are given in a trichotomous format (yes, limited a little; yes, limited a lot; no, not limited at all) for the final two questions.	X			X
Parental Quality of Life[42]	ICCAP: Thirty-two questions to assess the impact on parental quality of life. Four questions ask about contact with caregivers, six ask about support from social networks, five ask about partner relationships, four ask about the participant's state of mind, and the remaining thirteen ask about fear and anxiety. Answers range on a 4-point Likert scale that ranges from 1=strongly disagree to 4=strongly agree, with a "not applicable" option.			X	X
Decision Making Outcomes					
Preference for SDM[43]	Adaption of Degner & Sloagan's Control Preference Scale - A single question on how participants plan to make the decision. Responses include 1=My doctor(s) will make the decision with little input from me, 2=My doctor(s) will make the decision but will seriously consider my opinion, 3=My doctor(s) and I will make the decision together, 4=I will make the decision after seriously considering my doctor(s) opinion, 5=I will make the decision with little input from my doctor(s).	X	X		X

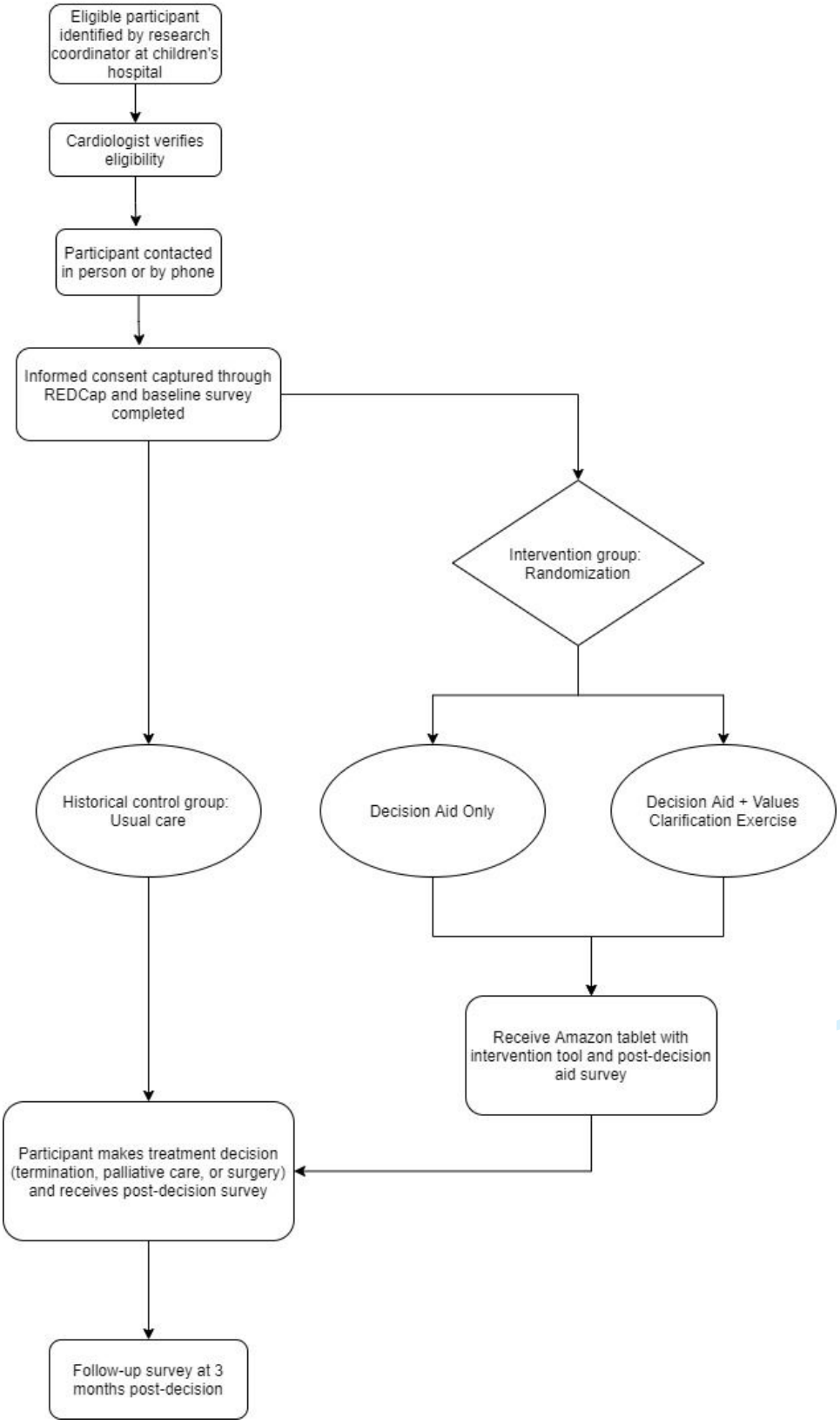
Preparation for Decision Making[44]	A validated scale which will assess participants' perspectives of the decision aid's usefulness in preparing them to communicate with their clinicians and for Shared Decision Making. These questions are answered on a Likert scale ranging from 1=not at all to 5=a great deal.		X		
Decision Self-Efficacy[45]	Eleven questions to assess self-efficacy for making an informed choice (e.g., getting needed information, asking questions, expressing opinions) using a 5-point Likert scale ranging from 0=not at all confident to 4=extremely confident.	X	X	X	
Decision Conflict[46]	Sixteen questions measuring: 1) perceptions of uncertainty in choosing options, 2) feelings of having adequate knowledge and clear values, and 3) effective decision making. All items use a 5-point Likert scale ranging from 0=strongly disagree to 4=strongly agree.		X	X	X
Decision Regret[47]	Five questions asking participants to reflect on the decision they made about which treatment option they chose for their child. All questions assessed on a 5-point Likert scale from 1=strongly disagree to 5=strongly agree.				X
Use of Information Sources	Extent that participants consulted any of 10 sources of health information. 2 sources are about personal relationships (i.e., relatives and friends), 3 are about mass media (i.e., exposure to television/movies, magazines, and books about CHD), 2 are educational/research sources (e.g., scientific journals) and the remaining 3 are about providers, support groups, and other parents who have a child with CHD. Answers rated on a 5-point Likert scale ranging from 1=never to 5=a great deal.		X		

Treatment Choice	Treatment Choice will be assessed by asking participants to identify which treatment they chose. Using electronic health records, we will record the child's actual treatment in case of parental change of mind or misreport.		X	X	X
Acceptability of Decision Aid	Participants answered five questions about if they used the decision aid (DA) before their appointment or during their appointment, their likelihood to recommend the DA, the amount of information presented, and if the DA seemed biased.		X		
Clinical Encounter Outcomes					
COMRADE[48]	Ten questions on 5-point scale (1=strongly disagree, 5=strongly agree) to evaluate the participant's perspective of the effectiveness of risk communication and treatment decision making in clinician consultations.		X	X	
Consultation Quality[49]	Participants complete 2 questions that measure the quality of consultation. One measures the perceived usefulness of consultation on a 7 point Likert scale that ranges from 0=not at all useful to 6=very useful. The second question measures participants' perspective regarding whether the clinician was biased towards any certain treatment.	X			X
Parents' Characteristics and Survey Feedback					
Demographics	Participants indicate their gender, education, race, ethnicity, number of children, religion, religiosity, marital status, and whether or not they have health insurance.	X			
Literacy[50]	Three validated, brief questions identifying participants with inadequate health literacy.	X			

Numeracy[51]	A validated scale of 8 questions that distinguish an individual's quantitative ability without asking overly-invasive questions. Answers are rated on a 6-point Likert scale ranging from 1=not at all good/never to 6=extremely good/very often for six questions, 1=always prefer percentages to 6=always prefer numbers for one question, and 1=always prefer percentages to 6=always prefer words for one question.	X			
Religiosity[52]	Two items asking "How often do you attend church or other religious meetings" (1=Never to 6=More than once/week) and "How often do you spend time in private religious activities, such as prayer, meditation or Bible study" (1=Rarely or never to 6=More than once a day)	X			
Assessing Survey Burden	Six yes/no questions asked if the survey had burdensome questions, one 5-point Likert scale question asked about how useful the participant perceived the survey would be (1=not at all useful and 5=very useful), two 5-point Likert scale questions asked participants to rate how burdensome/time consuming the survey was from 1=time consuming/burdensome to 5=quick/easy.	X	X	X	X

Note: Time 1= at diagnosis, Time 2= post-receipt of decision aid, Time 3= post-decision, Time 4= 3 months post- decision

Figure 1. Study Timeline



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1

	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	26
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16-17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17

	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol

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A Study Protocol for a Randomized Clinical Trial of a Decision Aid and Values Clarification Method for Parents of a Fetus or Neonate Diagnosed with a Life-Threatening Congenital Heart Defect

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A Study Protocol for a Randomized Clinical Trial of a Decision Aid and Values Clarification Method for Parents of a Fetus or Neonate Diagnosed with a Life-Threatening Congenital Heart Defect

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Contributorship Statement: All authors have contributed to the design of this protocol. RD, NP, EO, LS, HW, PT, and AF initiated and conceptually designed the project. MP, LH, LL, and NP are acquiring data. The protocol was drafted by RD and MP and was refined by for critically important content by RD, AT, NP, EO, MP, LS, LH, LL, HW, PT, and AF. Statistical advice was provided by TG. AF obtained funding for the study. All authors contributed to the manuscript and read and approved the final manuscript.

Trial registration: NCT04437069

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Conflict of Interest Disclosures: The authors have no conflicts of interest to disclose.

Abstract

Introduction: Parents who receive the diagnosis of a life-threatening, complex heart defect in their fetus or neonate face a difficult choice between pursuing termination (for fetal diagnoses), palliative care, or complex surgical interventions. Shared decision making (SDM) is recommended in clinical contexts where there is clinical equipoise. SDM can be facilitated by decision aids. The International Patient Decision Aids Standards collaboration recommends the inclusion of values clarification methods (VCMs), yet little evidence exists concerning the incremental impact of VCMs on patient or surrogate decision making. This protocol describes a randomized clinical trial to evaluate the effect of a decision aid (with and without a VCM) on parental mental health and decision making within a clinical encounter.

Methods and Analysis: Parents who have a fetus or neonate diagnosed with one of six complex congenital heart defects at a single tertiary center will be recruited. Data collection for the prospective observational control group was conducted September 2018 to December 2020 (N=35) and data collection for two intervention groups is ongoing (began October 2020). At least 100 participants will be randomized 1:1 to two intervention groups (decision aid only vs. decision aid with VCM). For the intervention groups, data will be collected at four time points: 1) at diagnosis, 2) post-receipt of decision aid, 3) post-decision, and 4) 3-months post-decision. Data collection for the control group was the same, except they did not receive a survey at Time 2. Linear mixed effects models will assess differences between study arms in distress (primary outcome), grief, and decision quality (secondary outcomes) at 3-months post-treatment decision.

Ethics and Dissemination: This study was approved by the University of Utah Institutional Review Board and the protocol is published on ClinicalTrials.gov (NCT04437069). Study findings have and will continue to be presented at national conferences and within scientific research journals.

Article Summary

Strengths and limitations of this study:

- One study strength is that this is a randomized clinical trial design with clinically relevant, validated outcome measures.
- A second strength is that this study will add to the limited literature on the effectiveness of value clarification methods in real-word clinical contexts.
- Given that the study takes place at one tertiary center, there is potential limitation of decreased diversity of the sample, a small sample size, and reduced power for analyses.

Introduction

Background and rationale

Congenital heart disease occurs for about 40,000 live births per year; of these, about 2-3% are life-threatening congenital heart defects (CHDs).[1-3] Even with early intervention those diagnosed with life-threatening CHDs have frequent readmissions, require additional interventions and typically face a shortened life span.[4] A diagnosis of a severe, life-threatening CHD in a fetus or neonate is an unexpected and emotionally distressful event for parents who must then decide between termination (when diagnosed prenatally), palliative care, or surgery.[5-8] Parents experience significant grief,[9,10] distress, depression, and anxiety[11-13] surrounding this difficult decision, which can compromise their mental health.[14-16]

Shared decision making (SDM) is an approach for supporting patient engagement with clinicians that is particularly useful for contexts, such as life-threatening CHD, which involve clinical equipoise and value-laden, complex decisions.[17-21] Decision aids are tools that improve the SDM process and include information on treatment options that are evidence based, balanced, and help people clarify their values.[4,22] Decision aids increase patients' knowledge, and engagement related to the diagnosis and treatment decision making. In addition, studies have found greater concordance between patients' preferences and treatment received, improved patient-provider communication, and reduced uncertainty and decisional conflict in those receiving decision aids.[23]

The International Patient Decision Aids Standards (IPDAS) Collaboration developed criteria for a well-designed decision aid.[24] Values clarification methods (i.e., processes that aid patients in

clarifying their values and goals in order to improve alignment between their preferences and their treatments) were included as a critical component. Although some studies have found positive effects of value clarification methods on decision outcomes, there are few rigorous studies in real-world clinical contexts that evaluate whether value clarification methods improve key outcomes, prompting calls for additional research.[24-26]

Objectives & Hypothesis

The main objective of the study is to evaluate the effect of a decision aid with and without a values clarification method on longitudinal parent mental and physical health, decision-making, and clinical encounter outcomes (e.g., quality of clinician consultation and risk communication). Since no prior data on decision aid use in CHD exist, we will also compare parents who receive the decision aid to parents who do not (prospective observational control group enrolled during decision aid development) on the aforementioned outcomes.

We hypothesize that participants who receive the decision aid with the values clarification method will report less distress (primary outcome), reduced grief, and better decision quality (secondary outcomes) relative to participants who receive the decision aid only across 3-months post-treatment decision. We also hypothesize that participants who receive the decision aid with or without the values clarification method will report reduced distress, grief, and better decision quality relative to participants who are in the prospective observational control group.

We will also test the impact of the decision aid with a values clarification method on several exploratory measures (e.g. self-efficacy, satisfaction, and decision regret).

Methods

Study Design

This is a randomized clinical trial examining the effectiveness of a decision aid and values clarification method. There are two intervention groups and one prospective observational control group. Data collection for the prospective observational control group was conducted September 2018 – December 2020 (N= 35) and data collection for the intervention groups (the primary analytic sample) began October 2020 and is ongoing. The flow of the study is outlined in Figure 1.

Study Setting

This is a single site study at a children's hospital in the Intermountain West. Physicians at this hospital perform >650 fetal echocardiograms with about 125 new complex CHD diagnoses annually.

Participants and Eligibility Criteria

To be eligible for the study, parents must be 18+ who have a fetus or neonate diagnosed with a complex, life-threatening CHD (whether prenatally or postnatally). While the decision aid was being developed, the control group was recruited with these guidelines. The decision aid was developed to provide information on the following six CHD diagnoses: truncus arteriosus with greater than moderate truncal valve regurgitation, pulmonary atresia with intact ventricular septum with a severely hypoplastic right ventricle that will require single ventricle palliation, complex single ventricle, complex single ventricle with heterotaxy, hypoplastic left heart syndrome (HLHS), and Ebstein anomaly of the tricuspid valve with greater than moderate regurgitation. These diagnoses were chosen as they were deemed preference sensitive in that surgical intervention, palliative care, and termination were all medically reasonable treatment

options by expert consensus. Thus, in order to be eligible for one of the two intervention groups, the fetus/neonate must be diagnosed with one of the six aforementioned diagnoses.

Recruitment and Consent

When a fetus/neonate is diagnosed with a qualifying CHD, a pediatric cardiologist will evaluate the diagnosis to confirm eligibility for the study. Patients consult with a clinician immediately after the diagnosis. Then, they are approached by research staff for study participation. When an eligible fetus/neonate is identified, the parent(s) will be approached by the study team and invited to participate in the study. One or both parents may participate. Interested participants receive a link to complete the informed consent through an electronic data capture (REDCap). If both parents consent to participation, they will receive separate links to complete their own informed consent and surveys. For the intervention groups, the decision aid is initiated by the parent, independent of the provider or coordinator. Both the control and intervention groups consult with clinicians as they decide which treatment to pursue.

Randomization

Participants will be randomized using REDCap (HIPAA-compliant remote data capture system) into one of two intervention groups, described below, after completing the baseline survey. Participants will not be explicitly told which group they were randomized to. Both intervention groups will receive the same decision aid, but one arm will receive a values clarification method integrated within the decision aid, while the other group will get the decision aid without the values clarification method. The decision aid is an app on an Amazon Fire tablet, which is either given to the parent(s) in clinic if they complete the baseline survey and consent in person, or is mailed to their home if they complete the consent outside of clinic. The tablet remains in their

possession for the duration of the study so that they can consult the decision aid as often as they would like.

Development of Decision Aid and Values Clarification Method

We used data from focus groups of parents who had a fetus/neonate diagnosed with a complex CHD, as well as semi-structured interviews with family and provider stakeholders to identify important content to include in the digital decision aid.[27,28] The tool was developed through an iterative process of content drafting by the development team followed by multiple rounds of content review and revision with the research team, parent partners, and healthcare providers in relevant fields (e.g., pediatric cardiologists, surgeons, social workers, palliative care experts). The team gathered stories about parents' experiences during several individual and group interviews.

The research team also developed a values clarification method. We began by examining qualitative data from the focus group and interviews related to factors influencing parents' choices and identifying key elements that had influenced parents' decision. The team then engaged in multiple workshop sessions, discussing how best to describe components of each value, with parent partners providing input on draft versions of these descriptions. The values clarification method interface was developed through an iterative process of creating alpha versions, testing, and revision.

Patient and Public Involvement

Three parents (two females and one male) whose children were diagnosed with complex CHD were invited to serve as parent collaborators. Discussions with these parents informed the design and development of the decision aid, outcome measures that were chosen, and methods of recruitment for the study.

Interventions and Comparators

Prospective Observational Control Group

Participants in the prospective observational control group did not receive the decision aid or values clarification method. Participants were enrolled during the development of the decision aid to prevent contamination by providers or other families exposed to the decision aid. Participants received standard clinical care.

Decision Aid

The intervention group receives a decision aid after diagnosis and then continues with standard care. The decision aid includes eight sections, which are broadly described in Table 1. Section 5 is individualized to each participant to show information specific to their fetus/neonate's diagnosis. Participants are given the decision aid, which is an app that is loaded onto an Amazon Fire tablet (one per family).

Values Clarification Method

The Values Clarification Method is designed to help participants clarify the choice that feels better for them and their family. For those randomized to receive the values clarification method, the decision aid includes an extra module, *What Matters Most to You.* The goal of this exercise is to help participants think through some short- and long-term consequences of their decision. When faced with a life-threatening diagnosis, there are many consequences to consider, and participants may not know how they feel about each of them or how to weigh them by importance or value. To begin, participants choose two of the possible treatment decision options (surgery, comfort care, and ending the pregnancy) and compare them in 10 different topic areas. Some examples of the topics are: time in the hospital, the risk that the child will have impairments, financial issues, and life in adulthood. The purpose of choosing two potential

decisions at a time is to put them on a clear spectrum in a preference scale, as weighting all three at once would be too complicated in terms of determining weights. For each topic, there is a sliding scale between the two choices where they drag the slider to show how much they prefer one choice over another. At the end, they are shown a summary of which choice they preferred for each category. Participants are not issued a definitive result; the values clarification method allows them to look at a summary of their choices and draw their own conclusion about what they chose. They may repeat the exercise, selecting other options to compare.

After the interventions were developed in English, the decision aid and values clarification method were translated into Spanish by certified translators in the University of Utah's Office of Research Participant Advocacy (as were consent documents and survey measures).

Outcomes

All study measures were categorized into three conceptual domains: parental mental and physical health, decision-making quality, and clinical encounter (e.g., consultation quality) in Table 2. The primary outcome is distress, measured by the Brief Symptom Inventory Global Severity Index.[29] The co-secondary outcomes are perinatal grief and decision quality (i.e., adequate knowledge and concordance between participants' preferences and treatment decision).[30,31] Additional exploratory outcomes will also be measured. Descriptions of all study measures and time points for survey data collection are included in Table 2. Parent characteristics will be examined as potential covariates.

Sample Size and Power Calculation

At least 100 families will be randomized 1:1 to the two intervention groups, allowing up to two parents to participate per fetus/neonate. Our sample size calculations were based on the primary comparison between DA with and without the VCE. Based on our previous work,[32] we assume ≥

80% retention, a 3-month pre-post R ≥0.5, an average of ≥1.75 participating parents per participating family, an intra-class correlation (ICC) between parents in the same family ≤0.50, and ≥50 families randomized to each of the intervention groups (decision aid only and decision aid with values clarification method). Using these assumptions, the mixed effects model will provide 80% power with 2-sided α=0.05 to detect a mean difference in the primary outcome, distress, equal to 0.50 of 1 standard deviation. This represents a medium effect size in Cohen's terminology.[33] Assuming a pooled SD in the global distress of 0.56 units,[32] the 0.50 SDs represents a minimum detectable effect of 0.28 units.

Data Collection

Potentially eligible parents are identified by the provider. Following provider consultation, a study team member, trained in interacting with families going through highly emotional medical events, assesses if this is an appropriate time to approach them about the study. If the parents are too distressed, they are not approached at the time of the visit but asked if they would be willing to speak to research staff later. If the parents are deemed approachable by the trained staff, the study is presented using an informational pamphlet, and the potential participant(s) are encouraged to follow the link or QR code on the pamphlet if they would like to participate in the study. The parents who were given the link are recorded in a recruitment tracker. All parents who follow the link on their own are consented to participate in the study and recorded in REDCap. This usually happens with parents whose fetuses are prenatally-diagnosed, and they follow the link from their home electronic devices. If the neonate was postnatally-diagnosed, the parents are approached in the same manner in the hospital and are given the opportunity to consent and participate in the study using a tablet in person. Parents who are found to be ineligible or who decline participation will be recorded along with the reason.

Data Abstraction

When screening for eligibility, the fetus/neonate diagnosis (verified by a pediatric cardiologist) and date of diagnosis will be abstracted. Once enrolled in the study, gestational age at birth, the presence of other syndromes/birth defects, and the dates of surgery (if applicable) will be abstracted from the medical record and documented. Further surgery dates are recorded by the research coordinator.

Surveys

Participants in the prospective observational control group filled out surveys at three time points: 1) Baseline, 2) Post-Decision, and 3) Three Months Post-Decision (see Table 1 for an overview of measurements). There are four survey time points for the intervention groups: 1) Baseline, 2) Post-Viewing of the Decision Aid (or Decision Aid and Values Clarification Method) but prior to making the decision, 3) Post-Decision, and 4) Three Months Post-Decision. Surveys are administered via REDCap by sending an email to the participant with a survey link. Participants may request paper surveys to be mailed to them. If the participant does not access the survey link, they will be contacted by phone or in person during a routine clinic visit to ask them to fill out the survey or will be mailed a paper survey.

Data Management and Monitoring

Adverse events that occur during data collection will be recorded by the study coordinator, along with any circumstances that make particular participants unique. In this way, unanticipated data points during analysis may be explained and accounted for. Additionally, information about mental health resources are given to participants at the end of each survey, including a 24-hour, 7 days-a-week phone crisis service that is staffed by mental health professionals providing emotional support, assistance, crisis interventions, and suicide preventions to individuals

experiencing emotional distress or psychiatric crisis. The social worker at the children's hospital also has their contact information listed for participants to be able to reach out.

Frequent reports will be run to detect data errors or missing data. Any issues will be addressed during a weekly meeting between the study coordinator, post-doctoral fellow(s), and the principal investigator.

Data Analysis Plan

After data collection, we will use standardized mean differences to assess balance between intervention groups in baseline levels of study endpoints and other potential prognostic baseline indicators, including participants' age, race, and comorbidities. Outcome variables exhibiting substantial skewness may be transformed to better approximate normality. All participants will be analyzed in their assigned intervention group according to intention-to-treat, irrespective of adherence to viewing the decision aid or completing the values clarification method. Although multiple outcomes will be considered, we have designated a single primary outcome (the BSI Global Severity Index of global distress, described above) and a single primary comparison time for this outcome at 3 months.[34] We do not plan formal multiple comparison adjustments for secondary and exploratory outcomes. Results for secondary and exploratory outcomes will support or qualify the analyses of the primary outcome, and will be interpreted based on the overall pattern of results with awareness that some nominally significant relationships may be false positive findings in the context of multiple analyses. If there is sufficient power to detect differences, exploratory sub-group analyses may be conducted to detect differences by factors such as pre versus post-natal diagnoses, CHD diagnosis, provider specialty, and parent dyads. We also do not plan formal multiple comparison adjustment for the randomized comparison

between intervention groups (Decision Aid Only v. Decision Aid with Values Clarification Method) and the non-randomized comparison (Decision Aid v. Control), as these comparisons address distinct hypotheses and are thus appropriate for evaluation on a comparison wise basis.[35]

Determining Intervention Effects on Study Endpoints

Randomized Comparisons Between Intervention Groups (Decision Aid Only V. Decision Aid with Values Clarification Method). The primary outcome, distress, measured at post-decision aid, post-decision, and 3-month will be compared between groups by applying restricted maximum likelihood estimation to a linear mixed effects model[36] with fixed provider effects and random family effects to account for clustering of outcomes due to these factors and an unstructured residual covariance model to account for serial correlation across the three longitudinal assessments. Inclusion of fixed effects for provider is appropriate since families are randomized to the two intervention groups for each provider, and may improve statistical power by controlling for provider variation. The model will also include fixed effects for randomized assignment as well as the baseline distress.[34] Additional pre-specified covariate adjustment is not planned, as we are not aware of further baseline factors that are likely to have a strong association with the 3-month distress once the baseline distress is accounted for.[35] However, should a prognostic baseline factor exhibit imbalance between the randomized groups, a post-hoc sensitivity analysis will be performed with covariate adjustment for that factor to assess the robustness of the results to the imbalance. The 3-month comparison will represent the primary contrast for assessing the effect of the decision support intervention. It is possible that the full mixed effects model will fail to converge due to the inclusion of separate random effects for provider and family as well as an unstructured covariate matrix for repeated assessments in the same patient. In the event the full model fails to converge, we will repeat analyses after dropping

the provider random effect. If this also fails to provide convergence, the unstructured covariance model for serial correlation will be simplified.

Similar mixed effects analyses will be used for numeric secondary and exploratory outcome variables, including the perinatal grief (secondary outcome) and most of the exploratory outcomes. For binary outcomes, including the decision quality secondary outcome, we will apply generalized estimating equations (GEE) for log-binomial regression (if convergence is achieved) or modified Poisson regression[37] (if not) to compare the proportions of participants with the outcome between the intervention groups. The post-decision comparison will be the main comparison for evaluating the effects of the interventions on secondary and exploratory outcomes hypothesized to respond quickly to the decision aid (e.g. parent-provider communication, self-efficacy) while the 3-month comparison will represent the main treatment contrast for outcomes hypothesized to respond over a longer time (e.g., grief, decision regret).

Non-Randomized Comparisons of Decision Aid Only v. Control Group. The primary outcome, distress, will be compared between the groups receiving the decision aid and the control group using an extension of the linear mixed effects model described above. The model will again include fixed effects for provider and random effects for family and an unstructured covariance matrix to account serial correlation, but will be expanded to include all three treatment groups and will include not only the baseline distress measure but also timing of diagnosis, race, and literacy level as covariates to reduce bias in these non-randomized comparisons. The comparison of Decision Aid without Values Clarification Method vs. Control will represent the primary treatment comparison to evaluate the effect of the decision aid. The comparison of Decision Aid

with Values Clarification Method) vs. Control will provide a secondary assessment of the combined effect of decision support and values clarification method together. Similar extensions using linear mixed models for numeric outcomes and GEE for binary or categorical outcomes will be applied for additional non-randomized comparisons between the decision support and control groups.

*Missing Data***.** The proposed analyses of the primary and numeric secondary and exploratory outcomes apply likelihood-based inference and will thus remain approximately unbiased in the presence of missing data so long as the pattern of missingness follows a missing at random (MAR) mechanism.[38] To evaluate risk of bias from missing data patterns which depend on measured factors not included in the analytic models, participant characteristics will be compared between participants with complete data for the primary and main secondary outcomes and those participants with incomplete data. If substantial imbalances are detected, or if > 10% of participants have missing data for a primary or secondary outcome, multiple imputation will be used to impute missing outcome measurements. The multiple imputation will be performed with a Markov Chain Monte Carlo (MCMC) algorithm using an imputation model incorporating each analysis variable as well as auxiliary variables that are related to the probability of missingness.[39] Rubin's formulae will be used to account for the uncertainty introduced by the missing data. When data are missing for items within scales, we will use recommended imputation procedures rather than deleting participants listwise from the analysis.[38]

Ethics and Dissemination

This study was approved by the Institutional Review Board (IRB), and continues to be re-approved yearly according to the IRB's standards. Important modifications made to the data collection routine section of the IRB application will be reported in the findings if those changes are found to have impacted the data.

Consent to participate in the study is obtained from participants when they fill out the baseline survey. As this is a low-risk study, no signature is required. All survey data will be de-identified before sharing the results, posing no risk to participant confidentiality. Access to the data may be granted to outside parties on a case-by-case basis by the discretion of the PI. The study is registered on ClinicalTrials.gov (NCT04437069) where the public can access the full protocol. Study modifications and results will also be reported on ClinicalTrials.gov. In addition, findings will be disseminated through presentations at scientific meetings and publications in peer-reviewed journals.

Discussion

Parents of a fetus or neonate diagnosed with a life-threatening congenital heart defect are confronted with a significant and challenging decision between termination (when diagnosed prenatally), palliative care, or surgery.[5-8] This preference-sensitive decision should be supported through shared decision making whereby the family and providers can mutually engage in treatment decision making which is driven by what matters most to families and understanding of the diagnosis and treatment options.[20,21] Decision aids are one approach to facilitate shared decision making.[40] The present study aims to evaluate the effect of a novel, family-centered decision aid on parent mental and physical health, decision-making, and clinical encounter

outcomes. Few studies have examined how effective values clarification methods, which the International Patient Decision Aids Standards collaborative added as criteria for decision aids, are when combined with a decision aid in clinical contexts.[26] Therefore, this study also aims to contribute to the literature by examining the effect of the decision aid with and without a values clarification method.

There are some potential study limitations to note that are common when studying pediatric conditions. There may be issues with meeting sample size requirements for sufficient statistical power. This issue could arise due to the rarity of severe CHD diagnoses and the potential for high attrition as parents are under high emotional burdens and distress surrounding the diagnosis, decision, and coping or managing the treatment they choose. Our study design attempts to proactively address these issues. For instance, we will use extensive follow-up procedures via telephone or in person to minimize attrition. If questionnaire burden results in higher than expected attrition, we will limit questions to the primary and secondary outcomes.

Our study will significantly contribute to advancing decision support and counseling for parents making life-altering decisions for their fetus or neonate with a life-threatening heart defect. This important and innovative decision aid and values clarification method will also build on the dearth of decision aids in pediatric, surrogate decision-making contexts.

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Table 1. Decision Aid Content

1. *You Are Not Alone*	This introductory video (07:53 min), is intended to normalize the experience and set the stage before some of the more technical information in the tool. Key messages are: this is a difficult time for you, it's OK to cry, you didn't cause this, and you are the most qualified to make this decision. The video also describes the goals of the tool.
2. *How the Heart Works*	This section includes animations and information on the cardiovascular system, normal fetal and post-fetal heart circulation, defects that can take place during heart development that lead to abnormal heart function, and a glossary of medical terms.
3. *What is a Congenital Heart Defect?*	This section defines congenital heart defects and how they are caused and diagnosed.
4. *How We Talk About Congenital Heart Defects*	This section introduces parents to topics and terms that are often used when discussing congenital heart defects, including statistics, diagnosis variability, survival and quality of life (e.g., developmental delay in cognitive abilities)
5. *Learn More About Your Baby's Diagnosis*	This section shows parents individualized information specific to their fetus/neonate's diagnosis. Diagnoses available in this section include Hypoplastic Left Heart Syndrome (HLHS), Complex Single Ventricle (CSV), Complex Single Ventricle with Heterotaxy (Isomerism), Pulmonary Atresia with Intact Ventricular Septum (PA/IVS), Ebstein's Anomaly of the Tricuspid Valve (With Severe Leak) and Truncus Arteriosus. Each diagnosis profile includes animated videos depicting the defect, statistics related to how common the defect is, other associated conditions, risks of having another child with the defect and expected outcomes without treatment.
6. *Learn More About Your Choices*	This is divided into three sections: Surgery, Comfort Care, and Ending the Pregnancy. Each section begins with a "What to Expect" overview and includes a description of the medical team members who may be involved, financial implications, living with this decision, and links to other websites and

	support groups. Additional information is tailored to each choice.
7. *Firsthand Experiences*	This section contains stories from parents who chose Comfort Care, Surgery or Ending the Pregnancy, in which they describe their personal experiences. Five stories are provided for each of the three choices, reflecting a variety of different outcomes. Surgery stories include examples where the child had no serious medical complications growing up, examples where the child does have complications, and examples where the child did not survive post-surgery.
8. *Questions You Can Ask Your Doctor*	This is a list of possible questions parents may wish to ask care providers. Parents can checkmark the questions they wish to take with them to their doctor, and the tool will email them just these questions. They can then either print or access their questions digitally while in their appointment.

Table 2. Study Outcomes, Descriptions, and Survey Measure Time Points

Measure	Description	Measure Timepoints			
		Time 1	Time 2	Time 3	Time 4
Primary Outcome					
Mental and Physical Health Outcomes					
Distress[29]	Basic Symptom Inventory (BSI) Global Severity Index of Global Distress: a validated scale of 53 questions that indicate the degree of stress the participant has experienced within the previous seven days. Answers range on a 5-point Likert scale from 0=not at all to 4=extremely.	X	X	X	X
Secondary Outcomes					
Decision Making Outcomes					
Perinatal Grief[30]	Twenty-seven questions measuring grief, coping, and despair following the death of a child. Rated on a 5-point Likert scale that ranges from 1=strongly disagree to 5=strongly agree.				X
Decision Quality (Values)[31]	Six questions on parent' decisional values (e.g., "How important it is to you that your child have as little pain and discomfort from treatment as possible?") rated on a 6-point Likert scale from 1=most important to 6=not as important.		X	X	X
Decision Quality (Knowledge)[31]	Twenty-six questions assessing the participants' knowledge of treatment options for CHD in two domains. The first domain regards understanding about CHD diagnosis and what the heart does, the available options, and the outcomes of comfort care. The second domain regards understanding about the outcomes of surgery/intervention and the impact of CHD on family. 21 of the questions use a dichotomous response format (either "true / false" or "yes/no"); 5 questions are multiple choice.		X	X	X

Exploratory Outcomes					
Mental and Physical Health Outcomes					
Mental and Physical Functional Health[41]	SF-12: Twelve items measuring the respondents' health across multiple dimensions. Answers rated on a 5-point Likert scale ranging from 1=excellent to 5=poor for three questions; answers are given in a dichotomous (yes/no) format for four questions; answers are given on a 6-point Likert scale ranging from 1=all of the time to 6=none of the time for three questions; answers are given in a trichotomous format (yes, limited a little; yes, limited a lot; no, not limited at all) for the final two questions.	X			X
Parental Quality of Life[42]	ICCAP: Thirty-two questions to assess the impact on parental quality of life. Four questions ask about contact with caregivers, six ask about support from social networks, five ask about partner relationships, four ask about the participant's state of mind, and the remaining thirteen ask about fear and anxiety. Answers range on a 4-point Likert scale that ranges from 1=strongly disagree to 4=strongly agree, with a "not applicable" option.			X	X
Decision Making Outcomes					
Preference for SDM[43]	Adaption of Degner & Sloagan's Control Preference Scale - A single question on how participants plan to make the decision. Responses include 1=My doctor(s) will make the decision with little input from me, 2=My doctor(s) will make the decision but will seriously consider my opinion, 3=My doctor(s) and I will make the decision together, 4=I will make the decision after seriously considering my doctor(s) opinion, 5=I will make the decision with little input from my doctor(s).	X	X	X	

Preparation for Decision Making[44]	A validated scale which will assess participants' perspectives of the decision aid's usefulness in preparing them to communicate with their clinicians and for Shared Decision Making. These questions are answered on a Likert scale ranging from 1=not at all to 5=a great deal.		X		
Decision Self-Efficacy[45]	Eleven questions to assess self-efficacy for making an informed choice (e.g., getting needed information, asking questions, expressing opinions) using a 5-point Likert scale ranging from 0=not at all confident to 4=extremely confident.	X	X	X	
Decision Conflict[46]	Sixteen questions measuring: 1) perceptions of uncertainty in choosing options, 2) feelings of having adequate knowledge and clear values, and 3) effective decision making. All items use a 5-point Likert scale ranging from 0=strongly disagree to 4=strongly agree.		X	X	X
Decision Regret[47]	Five questions asking participants to reflect on the decision they made about which treatment option they chose for their child. All questions assessed on a 5-point Likert scale from 1=strongly disagree to 5=strongly agree.				X
Use of Information Sources	Extent that participants consulted any of 10 sources of health information. 2 sources are about personal relationships (i.e., relatives and friends), 3 are about mass media (i.e., exposure to television/movies, magazines, and books about CHD), 2 are educational/research sources (e.g., scientific journals) and the remaining 4 are about providers, support groups, other parents who have a child with CHD, and spiritual or religious advisor. Answers rated on a 5-point Likert scale ranging from 1=never to 5=a great deal.		X		

Treatment Choice	Treatment Choice will be assessed by asking participants to identify which treatment they chose. Using electronic health records, we will record the child's actual treatment in case of parental change of mind or misreport.		X	X	X
Acceptability of Decision Aid	Participants answered five questions about if they used the decision aid (DA) before their appointment or during their appointment, their likelihood to recommend the DA, the amount of information presented, and if the DA seemed biased.		X		
Clinical Encounter Outcomes					
COMRADE[48]	Ten questions on 5-point scale (1=strongly disagree, 5=strongly agree) to evaluate the participant's perspective of the effectiveness of risk communication and treatment decision making in clinician consultations.			X	
Consultation Quality[49]	Participants complete 2 questions that measure the quality of consultation. One measures the perceived usefulness of consultation on a 7 point Likert scale that ranges from 0=not at all useful to 6=very useful. The second question measures participants' perspective regarding whether the clinician was biased towards any certain treatment.	X		X	
Parents' Characteristics and Survey Feedback					
Demographics	Participants indicate their gender, education, race, ethnicity, number of children, religion, marital status, and whether or not they have health insurance.	X			
Literacy[50]	Three validated, brief questions identifying participants with inadequate health literacy.	X			

Numeracy[51]	A validated scale of 8 questions that distinguish an individual's quantitative ability without asking overly-invasive questions. Answers are rated on a 6-point Likert scale ranging from 1=not at all good/never to 6=extremely good/very often for six questions, 1=always prefer percentages to 6=always prefer numbers for one question, and 1=always prefer percentages to 6=always prefer words for one question.	X			
Religiosity[52]	Two items asking "How often do you attend church or other religious meetings" (1=Never to 6=More than once/week) and "How often do you spend time in private religious activities, such as prayer, meditation or Bible study" (1=Rarely or never to 6=More than once a day)	X			
Assessing Survey Burden	Six yes/no questions asked if the survey had burdensome questions, one 5-point Likert scale question asked about how useful the participant perceived the survey would be (1=not at all useful and 5=very useful), two 5-point Likert scale questions asked participants to rate how burdensome/time consuming the survey was from 1=time consuming/burdensome to 5=quick/easy.	X	X	X	X

Note: Time 1= at diagnosis, Time 2= post-receipt of decision aid, Time 3= post-decision, Time 4= 3 months post- decision

Figure 1: Study Flow

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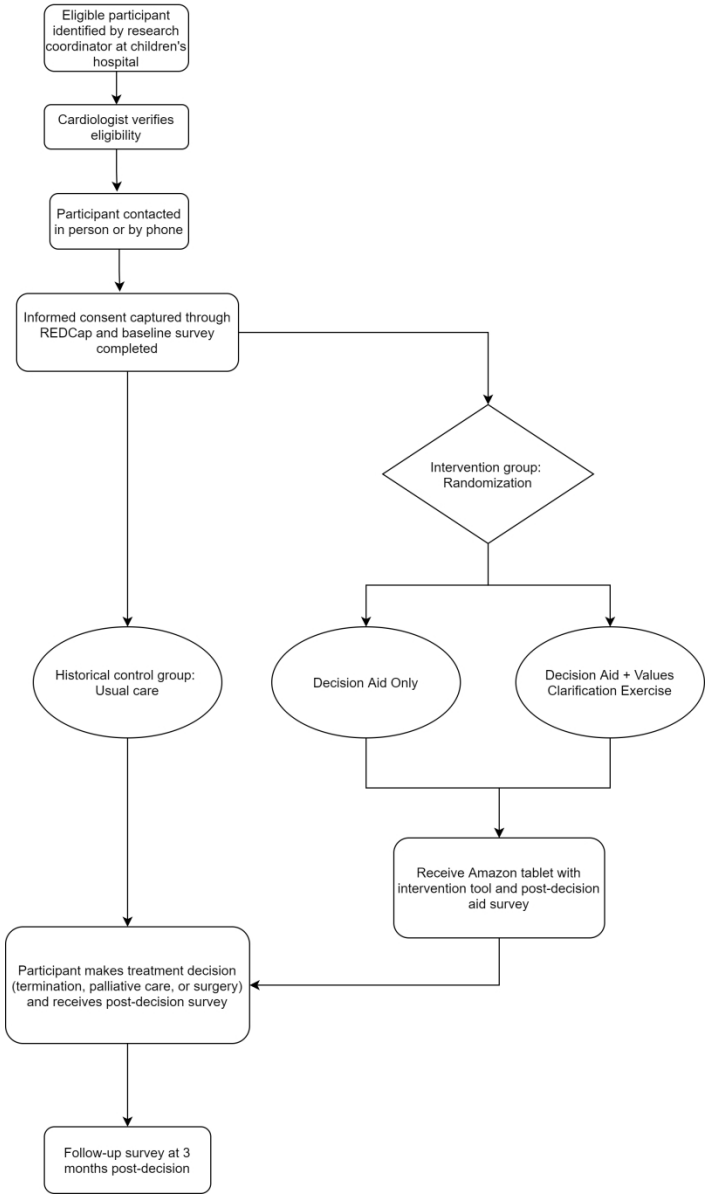

Figure 1: Study Flow

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1

	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	26
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16-17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17

	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol

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